SERUM URIC ACID – AN INDEPENDENT RISK FACTOR IN ACUTE NON-EMBOLIC ISCHAEMIC STROKE

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CERTIFICATE

This is to certify that this dissertation titled **"SERUM URIC ACID – AN INDEPENDENT RISK FACTOR IN ACUTE NON-EMBOLIC ISCHAEMIC STROKE"** submitted by **Dr. P. RAMANATHAN** to the faculty of General Medicine, The Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of MD degree Branch I (General Medicine) is a bonafide research work carried out by him under our direct supervision and guidance.

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DECLARATION

I, **Dr. P. RAMANATHAN**, solemnly declare that the dissertation titled **"SERUM URIC ACID – AN INDEPENDENT RISK FACTOR IN NON-EMBOLIC ISCHAEMIC STROKE"** has been prepared by me.

This is submitted to the Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment of the regulations for the award of MD Degree Branch I (General Medicine).

It was not submitted to the award of any degree/ diploma to any University either in part or in full form previously.

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CONTENTS

ABBREVIATIONS AND ACRONYMS

SUA	–	Serum Uric Acid
HTN	–	Hypertension
DM	–	Diabetes Mellitus
Met S	–	Metabolic Syndrome
CT	–	Computerized tomography
Echo	–	Echocardiogram
ECG	–	Electrocardiogram
CVA	–	Cerebro Vascular Accident
CV Risk	-	Cardio Vascular Risk
NO	-	Nitric Oxide
IR	-	Insulin Resistance
IFG	-	Impaired Fasting Glucose
IGT	-	Impaired Glucose Tolerance

INTRODUCTION

Among all the neurological diseases of adult life, the cerebrovascular ones clearly rank the first in frequency and importance. Atleast 50% of the neurological disorders in a general hospital are of this type. Stroke, after heart disease and cancer is the most common cause of death. In the developed countries among 700000 cases of stroke, roughly 600000 are ischemic lesions. All the physicians have a role to play in the prevention of stroke by encouraging the reduction in risk factors(1). Stroke also entails a high socio economic burden due to increased morbidity and mortality(2).Ischemic strokes account for > 80% of total stroke events. Early identification of individuals at risk could be of help in primary prevention strategies(3).

UA is the most abundant aqueous antioxidant in humans, and contributes as much as two-thirds of all free radical scavenging capacity in plasma. It is particularly effective in quenching hydroxyl, superoxide and peroxynitrite radicals, and may serve a protective physiological role by preventing lipid peroxidation(34). In a variety of organs and vascular beds, local UA concentrations increase during acute oxidative stress and ischaemia, and the increased concentrations might be a compensatory mechanism that confers protection against increased free radical activity (64). In animal models, local UA concentrations significantly increase in acute brain

injury(62).For example, in the rat, middle cerebral artery occlusion causes a significant increase in cerebral UA concentrations, which can persist for several days after the injury(63). These observations have prompted interest in the potential impact of raised local UA concentrations in the setting of acute ischaemic stroke.

The role of serum uric acid (SUA) levels as an independent risk factor for vascular disease has been questioned for decades(4). Evidence from epidemiological studies suggest that the elevated SUA levels may predict an increased risk for cerebrovascular (CV) events including stroke (4-7). Moreover therapeutic modalities with a SUA lowering potential have been shown to reduce CV disease morbidity and mortality (8).

Subjects with NIDDM have a two fold to four fold greater risk of all manifestations of atherosclerotic vascular disease including stroke (10). The increased risk of stroke is only partly explained by the adverse effects of NIDDM on classic risk factors or risk factors clustering with hyperinsulinemia(10). SUA has been recently associated with insulin resistance(11).One study (10) indicates that hyperuricemia is a strong predictor of stroke events in middle aged patients with NIDDM independent of other CV risk factors.

Although high SUA levels have been identified as an important risk factor for stroke in unselected populations in a number of epidemiological studies (4-7), it is unclear whether high SUA levels promote or protect against the development of CV disease or simply acts as a passive or circumstantial marker of increased risk(12). However data from larger studies (NHANES I) have established an independent association in subjects older than 45, regardless of confounding factors such as sex, menopausal status , diuretic use, presence of CV disease or race(13).

In this respect SUA levels could be used as an easy to measure serum marker in selecting and appropriately treating subjects at risk(9).

REVIEW OF LITERATURE

URIC ACID(16)

Background

Uric acid is the final product of purine metabolism in human beings. Despite the fact that uric acid was first identified approximately 2 centuries ago, certain pathophysiologic aspects of hyperuricemia are still not clearly understood. For years, hyperuricemia has been identified with or thought to be the same as gout, but uric acid has now been identified as a marker for a number of metabolic and hemodynamic abnormalities.

Unlike allantoin, the more soluble end product found in lower animals, uric acid is a poorly soluble end product of purine metabolism in humans. Human beings have higher levels of uric acid, in part, because of a deficiency of the hepatic enzyme, uricase, and a lower fractional excretion of uric acid. Approximately two thirds of total body urate is produced endogenously, while the remaining one third is accounted for by dietary purines. Approximately 70% of the urate produced daily is excreted by the kidneys, while the rest is eliminated by the intestines. However, during renal failure, the intestinal contribution of urate excretion increases to compensate for the decreased elimination by the kidneys.

The blood levels of uric acid are a function of the balance between the breakdown of purines and the rate of uric acid excretion. Theoretically, alterations in this balance may account for hyperuricemia, although clinically defective elimination accounts for most cases of hyperuricemia.

Pathophysiology

Uric acid in the blood is saturated at 6.4-6.8 mg/dL at ambient conditions, with the upper limit of solubility placed at 7 mg/dL. Urate is freely filtered at the glomerulus, reabsorbed, secreted, and then again reabsorbed in the proximal tubule. The recent cloning of certain urate transporters will facilitate the understanding of specific mechanisms by which urate is handled in the kidney and small intestines.

A urate/anion exchanger (URAT1) has been identified in the brush-border membrane of the kidneys and is inhibited by an angiotensin II receptor blocker, losartan. A human organic anion transporter (hOAT1) has been found to be inhibited by both uricosuric drugs and antiuricosuric drugs, while another urate transporter (UAT) has been found to facilitate urate efflux out of the cells. These transporters may account for the reabsorption, secretion, and reabsorption pattern of renal handling of urate.

Urate secretion does appear to correlate with the serum urate concentration because a small increase in the serum concentration results in a marked increase in urate excretion.

Hyperuricemia may occur because of decreased excretion (underexcretors), increased production (overproducers), or a combination of these two mechanisms.

Underexcretion accounts for most causes of hyperuricemia. Urate handling by the kidneys involves filtration at the glomerulus, reabsorption, secretion, and, finally, postsecretory reabsorption. Consequently, altered uric acid excretion can result from decreased glomerular filtration, decreased tubular secretion, or enhanced tubular reabsorption. While decreased urate filtration may not cause primary hyperuricemia, it can contribute to the hyperuricemia of renal insufficiency. Decreased tubular secretion of urate occurs in patients with acidosis (eg, diabetic ketoacidosis, ethanol or salicylate intoxication, starvation ketosis). The organic acids that accumulate in these conditions compete with urate for tubular secretion. Finally, enhanced reabsorption of uric acid distal to the site of secretion is the mechanism thought to be responsible for the hyperuricemia observed with diuretic therapy and diabetes insipidus.

Overproduction accounts for only a minority of patients presenting with hyperuricemia. The causes for hyperuricemia in overproducers may be either exogenous (diet rich in purines) or endogenous (increased purine nucleotide breakdown). A small percentage of overproducers have enzymatic defects that account for their hyperuricemia. These include a complete deficiency of hypoxanthine guanine phosphoribosyltransferase (HGPRT) as in Lesch-Nyhan syndrome, partial deficiency of HGPRT (Kelley-Seegmiller syndrome), and increased production of 5-phospho-alpha-d-ribosyl pyrophosphate (PRPP) activity. Accelerated purine degradation can result from rapid cell proliferation and turnover (blast crisis of leukemias) or from cell death (rhabdomyolysis, cytotoxic therapy). Glycogenoses types III, IV, and VII can result in hyperuricemia from excessive degradation of skeletal muscle ATP.

Combined mechanisms (underexcretion and overproduction) can also cause hyperuricemia. The most common cause under this group is alcohol consumption, which results in accelerated hepatic breakdown of ATP and the generation of organic acids that compete with urate for tubular secretion. Enzymatic defects such as glycogenoses type I and aldolase-B deficiency are other causes of hyperuricemia that result from a combination of overproduction and underexcretion.

New findings revealed that urate crystals can engage an intracellular pattern recognition receptor, the macromolecular NALP3 (cryopyrin) inflammasome complex. NALP3 inflammasome may result in interleukin 1 (IL-1) beta production, which, in turn, incites an inflammatory response. Inhibition of this pathway has the potential to be targeted for hyperuricemia-induced crystal arthritis.

Frequency

A Japanese study that used an administrative claims database to ascertain 10-year trends in the prevalence of hyperuricemia concluded that the prevalence of hyperuricemia in the overall study population increased during the 10-year follow-up. When stratified by age, the prevalence increased among groups older than 65 years in both sexes. In those younger than 65 years, men had a prevalence 4 times higher than that in women, but in those older than 65 years, the gender gap narrowed to 1:3 (female-to-male ratio) with gout and/or hyperuricemia.

Mortality / Morbidity

Hyperuricemia has been associated with increased morbidity in patients with hypertension and is associated with increased mortality in women and elderly persons. The cause for this is unknown, but hyperuricemia

is probably a marker for comorbid risk factors rather than a causative factor, per se.

Race

A high prevalence of hyperuricemia exists in indigenous races of the Pacific, which appears to be associated with a low fractional excretion of uric acid. African American persons develop hyperuricemia more commonly than white persons.

Sex

Hyperuricemia, and particularly gouty arthritis, are far more common in men than in women. Only 5% of patients with gout are female, but uric acid levels increase in women after menopause.

Age

The normal serum uric acid level is lower in children than in adults. The upper limit of the reference range for children is 5 mg/dL (0.30 mmol/L). The upper limit of the reference range for men is 7 mg/dL (0.42 mmol/L) and for women is 6 mg/dL (0.36 mmol/L). The tendency to develop hyperuricemia increases with age

Sources of uric acid

In many instances, people have elevated uric acid levels for hereditary reasons. Diet may also be a factor.

Purines are found in high amounts in animal food products, especially internal organs.

Examples of high purine sources include: sweetbreads, anchovies, sardines, liver, beef kidneys, brains, meat extracts (e.g Oxo, Bovril), herring, mackerel, scallops, game meats, and gravy.

A moderate amount of purine is also contained in beef, pork, poultry, fish and seafood, asparagus, cauliflower, spinach, mushrooms, green peas, lentils, dried peas, beans, oatmeal, wheat bran and wheat germ. Moderate intake of purine-containing food is not associated with an increased risk of gout.[1]

Serum uric acid can be elevated due to high fructose intake, reduced excretion by the kidneys, and high intake of dietary purine.

Fructose can be found in processed foods and soda beverages - in some countries, in the form of high fructose corn syrup.

Anti-oxidant capacity

Uric acid may be a marker of oxidative stress(17), and may have a potential therapeutic role as an antioxidant. On the other hand, like other strong reducing substances such as ascorbate, uric acid can also act as a peroxidant(18), particularly at elevated levels. Thus, it is unclear whether elevated levels of uric acid in diseases associated with oxidative stress such as stroke and atherosclerosis are a protective response or a primary cause(19).For example, some researchers propose that hyperuricemia-induced oxidative stress is a cause of metabolic syndrome(20). On the other hand, plasma uric acid levels correlate with longevity in primates and other mammals(17). This is presumably a function of urate's antioxidant properties

STROKE(68)

A Stroke (STRUCK BY THE HAND OF GOD) or cerebrovascular accident (CVA) is defined by the abrupt onset of neurological deficit that is attributable to a focal vascular cause. The clinical manifestations of stroke are highly variable because of the complex anatomy of brain and its vasculature.

Cerebral ischemia is caused by a reduction in blood flow that lasts longer than several seconds. Neurological symptoms are manifest within seconds because neurons lack glycogen, so energy failure is rapid. When blood flow is quickly restored, brain tissue can recover fully and the patient's symptoms are only transient, that is called Transient Ischemic Attack(TIA).Typically the neurological signs and symptoms of a TIA lasts for 5 to 15 min but by definition must last for < 24 hrs. If the cessation of flow lasts for more than a few minutes, infarction or death of brain tissue results. Stroke has occurred if the neurological signs and symptoms last for > 24 hrs.

Focal ischemia or infarction is usually caused by thrombosis of cerebral vessels themselves or by emboli from a proximal arterial source or the heart. Cerebral hemorrhage produces neurological symptoms by producing a mass effect on neural structures or from toxic effects of blood itself.

CEREBRAL BLOOD FLOW (68)

- Gray matter -75 ml / 100 gm / min
- White matter – 30 ml / 100 gm /min
- Oxygen consumption --- 3.5 ml / 100 gm / min
- Glucose utilization ---- 5 mg / 100 gm / min

Brain store of glucose lasts only for 2 min after cessation of blood flow. The oxygen stores lasts only for 8 to 10 sec after cessation of blood flow.

A fall in blood flow to zero causes death of brain tissue within 4 to 10 min. Tissue surrounding the core region of infarction is ischemic but reversibly dysfunctional and is referred as ischemic penumbra. The ischemic penumbra will eventually infarct if no change in flow occurs and hence saving the ischemic penumbra is the goal of thrombolytic therapy.

RISK FACTORS FOR STROKE

MAJOR RISK FACTORS(14):

THE most important established risk factor for stroke is AGE , and second is probably HYPERTENSION. Additional well established risk factors are

1. Gender (male > female)	7. Carotid bruits
2. Family history	8. Smoking
3. Diabetes mellitus	9. Increased haematocrit
4. Cardiac disease	10. Elevated fibrinogen level
5. Prior stroke	11. Haemoglobinopathy
6.Transient Ischemic attacks	12. Drug abuse such as cocaine

OTHER RISK FACTORS (15) :

1.Hyperlipidemia	9.Homocystinemia
2. Diet	10. Migraine
3. Oral contraceptives	11.Race
4. Sedentary life style.	12. Geographic location
5. Obesity	13. Season and climate
6. Peripheral vascular disease	14.Type A personality
7. HYPERURICEMIA	15. Alcohol consumption
8. Infections.	

Clinical presentation

Stroke should be considered in any patient presenting with an acute neurological deficit (focal or global) or altered level of consciousness. Patients' symptoms vary depending on the area of the brain affected and the extent of the damage.

. No features of the history can accurately distinguish between ischaemic and haemorrhagic stroke. But haemorrhagic stroke is perhaps more likely if the presentation includes features of raised intracranial pressure (such as nausea, vomiting, and headache). Seizures are also more common in hemorrhagic stroke than in ischaemic stroke, occurring in up to 28% of hemorrhagic strokes. Meningism, the symptoms of meningeal irritation associated with acute febrile illness or dehydration without actual infection of the meninges, may also result from blood in the ventricles after a haemorrhagic stroke. Four important stroke syndromes are caused by disruption of particular cerebrovascular distributions.

Anterior cerebral artery

This primarily affects frontal lobe function, which results in altered mental status, contralateral lower limb weakness and hypoaesthesia, and gait disturbance.

Middle cerebral artery

This commonly results in contralateral hemiparesis, contralateral hypoaesthesia, ipsilateral hemianopia, and gaze preference toward the side of the lesion. Agnosia, a loss in ability to recognise objects, persons, sounds, shapes or smells, in the absence of a specific sensory deficit or memory loss, is common.

Receptive or expressive aphasia may result if the lesion occurs in the dominant (mainly left) hemisphere. Neglect (behaviour as if the contralateral sensory space does not exist) may result when the lesion occurs in the parietal cortex.

Posterior cerebral artery

This affects vision and thought, producing homonymous hemianopia, cortical blindness, visual agnosia, altered mental status, and impaired memory.

Vertebrobasilar artery

It causes a wide variety of cranial nerve, cerebellar, and brainstem deficits. These include vertigo, nystagmus, diplopia, visual field deficits, dysphagia, dysarthria, facial hypoaesthesia, syncope, and ataxia. Loss of pain and temperature sensation occurs on the ipsilateral face and contralateral body.

PATHOPHYSIOLOGY OF STROKE(1)

Cerebral infarction basically comprises two pathophysiologic processes.

1. Loss in the supply of oxygen and glucose secondary to vascular occlusion.
2. array of cellular metabolism consequent to the collapse of energy producing processes ultimately with disintegration of cell membranes.

Vascular Factors :

In several animal species including macaque monkeys and gerbils the critical level of cerebral blood flow was 23 ml / 100 gm / min ; if, after short periods time ,CBF is restored to higher levels the impairment of function can be reversed . Reduction of CBF below 10 to 12 ml /100 gm / min causes infarction regardless of duration. The critical level of hypoperfusion that abolishes function and leads to tissue damage is therefore a CBF between 12 to 23 ml /100 gm / min . At this level EEG is slowed and below this level it becomes isoelectric . These biochemical abnormalities are reversed if the circulation is restored to normal level. Disturbance of calcium ion homeostasis and accumulation of free fatty acids interfere with full recovery. A CBF of 6 to 8 ml /100/gm /min causes marked ATP depletion, increase in extra cellular K^+ increase in intracellular calcium and cellular acidosis,

leading invariably to histological signs of necrosis. Free fatty acids are activated and destroy the phospholipids of neuronal membranes. Prostoglandins, leucotrienes and free radicals accumulate and intracellular proteins and enzymes are denatured.

Penumbra zone exists at the margin of an infarction ,but not all, and the degree of irreversible tissue damage is difficult to determine. The neurons in the pneumbra are considered to be “stunned” by moderate ischemia and subject to salvage if blood flow is restored in a certain period of time. As with infarction , the duration of ischemia plays a role. Some studies show that elevating the systolic blood pressure or improving the rheological flow properties of blood in small blood vessels by haemodilution improves flow in the penumbra, however with mixed success.

Metabolic Factors:

Excitatory neurotransmitters , particularly glutamate and aspartate , which are formed from glycolytic intermediates of the Kreb’s cycle, released by ischemic cells excite neurons and produce an influx of Na^{+} and Ca^{2+} , lead onto irreversible cell injury. This is currently a subject of active biochemical and clinical research. Additional biochemical events must be induced by ischemia, including the production of free radicals, which leads to peroxidation and disruption of the outer cell membrane. Clearly these cascade

of cellular events that lead to neuronal death is likely to be more complex than is currently envisioned.

However , the extent of neural tissue dysfunction is not dictated solely by the activation of these mechanisms in neurons. It is now clear that highly toxic influences are exerted on oligodendroglial cells in white matter during ischemia. Moreover , injury to both neurons and oligodendroglial cells in brain tissue is augmented by an inflammatory response to the initial injury, activating endothelial cells to express cell adhesion molecules that can attract additional inflammatory cells and up regulating levels of inflammatory proteases (eg..metalloproteases)and cytokines (eg. interleukins and chemokines).

CT Scan And Ischaemic Stroke

Within six hours of the onset of ischaemic stroke, most patients will have a normal computed tomography scan. After 6-12 hours, sufficient oedema may collect into the area of the stroke so that a region of hypo-density may be seen on the scan.

Radiological clues before this include:

- Insular ribbon sign (loss of definition of grey-white interface in the lateral margins of the insula due to oedema in the insular cortex; (fig 1)
- Hyperdense middle cerebral artery sign (fig 2)
- Hypoattenuation in the lentiform nucleus (fig 3)
- Sulcal obliteration
- Shifting due to oedema
- Loss of grey-white matter differentiation.

These are all due to an increasing level of oedema in the brain, however, they rely on a high level of expertise of the radiologist and are often not present. Computed tomography scans also may fail to show some parenchymal haemorrhages smaller than 1 cm as a result of low resolution.

Fig. 1 : Computer tomograph after ischaemic stroke, showing oedema in insular cortex, as shown by solid arrows (open arrows show normal side)

Fig . 2. Computed tomograph after ischaemic stroke, showing hyperdense middle cerebral artery sign.

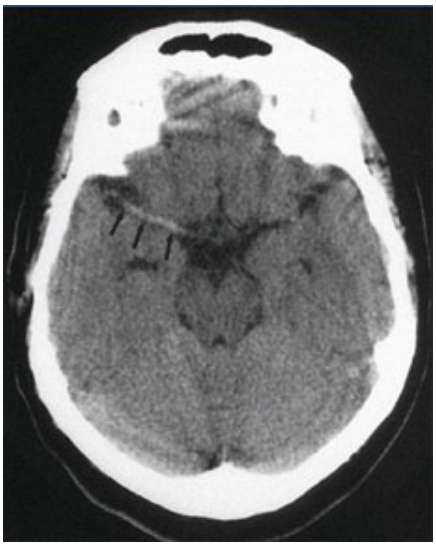


Fig .3. Computed tomograph after ischaemic stroke, showing hypoattenuation in the lentiform nucleus, as shown by solid arrows (open arrows show normal side).

SUA AND PATHOGENESIS OF STROKE

How UA may play a pathogenic role in stroke could be explained by experimental evidences. The possible mechanisms are as under.

SUA AND HYPERTENSION:

1. Elevated SUA level is an independent predictor of hypertension in 25 % of patients with new onset , untreated primary hypertension.(21)
2. The increase in SUA level may be caused by the decreased renal blood flow that usually accompanies the hypertensive state , because low renal blood flow stimulates urate reabsorbtion .(22)
3. Experimentally induced hyperuricemia also increased the blood pressure in rats by a renal mechanism linked to inhibition of nitric oxide (NO), activation of rennin- angiotensin system, and development of renal arteriosclerosis(23). Once the renal arteriosclerosis develops, the kidney plays a major role in the maintenance of hypertension, and lowering the UA is no longer protective.(24)
4. Prolonged hyperuricemia in rats also caused progressive renal injury via crystalline- independent mechanism (23) and accelerated established renal disease(25).

5. Finally UA stimulated synthesis of monocyte chemoattractant protein-1 by rat vascular smooth muscle cells(26) and this is known to stimulate macrophage infiltration of atherosclerotic vessels(27).

SUA AND FREE RADICAL MEDIATED OXIDATIVE DAMAGE – CEREBRAL ISCHEMIA

1. Cerebral infarction initiates a complex cascade of metabolic events in the surrounding tissue and free-radical-mediated oxidative damage plays a key role in the pathogenesis of cerebral ischemia (28). Free radicals are liberated from a variety of sources, including inflammatory cells, dysfunctional mitochondria and excitotoxic mechanisms stimulated by increased glutamate and aspartate concentrations(29)
2. Hydroxyl radicals, peroxynitrite and superoxide, are powerful radicals that can cause lipid peroxidation, a self –propagating chain reaction that irreversibly damages plasma and mitochondrial membranes(30). Products of lipid peroxidation irreversibly disrupt enzymes, receptors, and membrane transport mechanisms. The generation of local oxidants augments local injury and increases infarct size(28).
3. UA is the most abundant aqueous antioxidant in humans and may serve a protective physiologic role by preventing lipid peroxidation(34). It might therefore be expected that having elevated SUA levels during a stroke would be beneficial. Stroke is associated with a rapid decrease in

serum antioxidants(31,32) and patients with lower plasma antioxidants at the time of acute stroke have a poorer outcome(33). However, only one study has reported that high SUA levels may be neuroprotective in patients with acute stroke(35), three other large series found the opposite(6,7,9).

One explanation would be that UA, being an aqueous antioxidant, can become a pro-oxidant under certain circumstances, particularly if other antioxidants, such as ascorbate are low(36). Thus in patients with acute stroke the fall in ascorbate level could predispose the SUA to take on pro-oxidant properties. Consistent with this hypothesis is the observation that in acute stroke, those with high SUA and low ascorbate levels have the worst outcome(37).

SUA AND ENDOTHELIAL DYSFUNCTION:

Different studies support the hypothesis that hyperuricemia causes vascular disease via endothelial dysfunction. For example, direct infusion of UA into the human brachial artery caused endothelial dysfunction(38). UA was also found to promote LDL-C oxidation in vitro (39) and to stimulate granulocyte adherence to the endothelium(40).

In addition, a consistent relationship between elevated SUA levels and circulating inflammatory markers has been reported (41-43). Moreover UA may accumulate as crystals within atherosclerotic plaques(44).

SUA AND METABOLIC SYNDROME (Met S):

SUA might increase the risk of developing stroke through its association with the Met S (45,46). SUA levels are often increased in subjects with Met S (47-49).

1. Insulin Resistance (IR) is probably the underlying condition triggering the development of both hyperuricemia and Met S and it is directly related to SUA levels(45,50).
2. In patients with Met S, IR and decreased insulin-induced UA excretion may account for the observed increase in UA level(45).
3. IR may also be linked to purine biosynthesis and turnover with its attendant increase in UA levels(45,50).
4. SUA may promote or worsen IR possibily through its ability to disturb endothelial function and thus inhibit NO bioavailability (38).Because insulin requires NO to stimulate glucose uptake, it has been hypothesized that hyperuricemia may have a key role in the pathogenesis of IR (51).

5. In addition , a strong relationship between hyperuricemia and the risk factors of Met S has been shown in recent large epidemiological studies (48,52). Furthermore, Met S has recently been shown to represent a strong independent risk factor for ischemic stroke (53-56).
6. The prognostic value of increased SUA levels was independent of all the other criteria of Met S, pointing to a direct link between SUA levels and adverse outcome in acute stroke (57).

REDUCTION OF SUA AND PROTECTION AGAINST STROKE:

Beyond xanthine oxidase inhibitors like allopurinol and other uricosuric drugs (probenecid ,sulfinpyrazone), several other agents can decrease the SUA level, such as losartan and fenoifbrate (58). More importantly administration of statins significantly reduces SUA levels (59) and preserves renal function (60) and these actions independently protect against vascular events in high risk patients (49). Thus a reduction in SUA level could also partially explain the beneficial effects of statins against stroke (61).

The findings of LIFE study (Losartan Intervention for Endpoint Reduction in hypertension study) suggest that a decrease in SUA induced by losartan treatment attenuates CV risk, including stroke (8).

REFERENCE STUDIES

***1.Circ J* 2007; 71: 1120 – 1127**

Serum Uric Acid as an Independent Predictor of Early Death After Acute Stroke - Asterios Karagiannis, MD*; Dimitri P. Mikhailidis, MD**; Konstantinos Tziomalos, MD*;

Methods and Results Consecutive patients (n=435) presenting with ischemic stroke and intracerebral hemorrhage were included in the study

Conclusions Elevated levels of SUA are independently associated with an increased risk of early death in acute stroke.

***2.Stroke*. 2006;37:1503-1507**

Uric Acid Is a Risk Factor for Myocardial Infarction and Stroke - The Rotterdam Study : Michiel J. Bos, MD, MSc; Peter J. Koudstaal, MD, PhD; Albert Hofman, MD, PhD;

Methods—The study was based on 4385 participants of the Rotterdam Study who, at baseline (1990 to 1993), were _55 years of age, free from stroke and coronary heart disease, and had blood taken

Results—Average follow-up was 8.4 years. High serum uric acid levels were associated with risk of myocardial infarction and stroke

Conclusions—**Uric acid is a strong risk factor for myocardial infarction and stroke**

3.Atherosclerosis. 2006 Aug;187(2):401-7. : Serum uric acid and risk of ischemic stroke: the ARIC Study - Hozawa A,, Folsom AR, Ibrahim H

METHODS AND RESULTS: Of 15,792 ARIC participants, 13,413 who were free of recognized stroke or coronary heart disease (CHD) at baseline and had a baseline UA measurement were included in the analysis. We followed the participants for ischemic stroke incidence (N=381) over 12.6 years.

CONCLUSION: Our findings suggest that UA is an independent predictor of ischemic stroke among subjects not using diuretics, but that elevated UA itself may not cause ischemic stroke.

4.Diabetes Metab Res Rev. 2006 Jan-Feb;22(1):79-82 : Elevated serum urate concentration independently predicts poor outcome following stroke in patients with diabetes - Newman EJ, Rahman FS, Lees KR

METHODS: We studied a cohort of type 2 diabetes patients presenting to our unit with computed tomography-confirmed acute stroke. Fasting blood samples were drawn within 24 h of admission for urate concentration and standard battery of biochemistry and hematological tests

CONCLUSION: Elevated urate concentration is significantly and independently associated with increased risk of future vascular events in

diabetic stroke patients. Further studies to elucidate the mechanism of this observation are required

5.Journal of Internal Medicine 2005; 258: 435–441: Serum uric acid levels and risk for acute ischaemic nonembolic stroke in elderly subject - H. J . Milionis, K. J. Kalantzi, J. A. Goudevenos, K. Seferiadis

Objectives A total of 163 patients aged older than 70 years (88 men and 75 women) admitted due to a first-ever-in-a-lifetime acute ischaemic/nonembolic stroke and 166 volunteers (87 men and 79 women) without a history of CV disease were included. The association between SUA and stroke was determined by multivariate logistic regression modelling after adjusting for potential confounding factors.

Conclusion. Elevated SUA is associated with an increased risk for acute ischaemic/nonembolic stroke in a strictly defined population of elderly individuals independently of concurrent metabolic derangements. This association may need to be considered when treating the elderly

6.Int J Cardiol. 2005 Mar 18;99(2):269-75. : Risk factors for first-ever acute ischemic non-embolic stroke in elderly individuals - Milionis HJ, Liberopoulos E, Goudevenos J,

METHODS: A population-based case-control study of patients admitted to the University Hospital of Ioannina, Epirus, Greece, due to first-ever

ischemic/non-embolic stroke from March 1997 to January 2002. All patients were subjected to brain CT and had their serum lipids and biochemical metabolic parameters determined within 24 h from the onset of symptoms. Multivariate logistic regression analysis identified diabetes mellitus (odds ratio (OR), 1.92; 95% CI, 1.02-3.63), triglycerides (TG) (OR, 1.16; 95% CI, 1.09-1.22), HDL-cholesterol (OR, 0.57; 95% CI, 0.43-0.76), apo A-I (OR, 0.80; 95% CI, 0.70-0.92), lipoprotein(a) [LP(a)] (OR, 1.51; 95% CI, 1.25-1.79**), uric acid (OR, 1.30; 95% CI, 1.06-1.59**) albumin (OR, 0.38; 95% CI, 0.20-0.70) fibrinogen (OR, 1.10; 95% CI, 1.05-1.13) and the metabolic syndrome (OR 2.48, 95% CI, 1.16-5.29) as significantly associated with ischemic/non-embolic stroke.

7.***Stroke*** **2003;34;1956-1957 : Editorial comment - Elevated Uric Acid and Ischemic Stroke: Accumulating Evidence That It Is Injurious and Not Neuroprotective -** John Kanellis and Richard J. Johnson

There is also a potential pathogenetic mechanism to explain why an elevated serum uric acid at the time of stroke may be injurious. Recent evidence suggests that acute ischemic stroke results in generation of local oxidants that augment local injury and increase infarct size. Acute stroke is associated with a rapid decrease in serum antioxidants that recover slowly over the subsequent week. Individuals with lower plasma antioxidants at the time of acute stroke have a poorer outcome.

Uric acid is often considered an antioxidant and has been shown to scavenge hydrogen peroxide and hydroxyl radicals, to block nitrotyrosine formation from peroxynitrite, and to preserve extracellular superoxide dismutase.

One might therefore expect that having elevated uric acid during an acute stroke would be beneficial. One explanation is that uric acid, being an aqueous antioxidant, can become a pro-oxidant under certain circumstances, particularly if other antioxidants such as ascorbate are low. Thus, the fall in ascorbate (vitamin C) levels with acute stroke could predispose the serum uric acid to take on pro-oxidant properties. Consistent with this hypothesis is the observation that in acute stroke, those with high uric acid and low ascorbate levels have the worst outcome.

***8.Stroke*. 2003;34:1951-1957: Serum Urate as an Independent Predictor of Poor Outcome and Future Vascular Events After Acute Stroke -** Christopher J. Weir, PhD; Scott W. Muir, MBChB, MRCP;

Methods—In patients with ischemic stroke or primary intracranial hemorrhage, we determined the association of urate level with 90-day placement (alive at home, good outcome; dead or living in care, poor outcome)

Results—We studied 3731 patients and measured serum urate in 2498.

Conclusions—Independently of other prognostic factors**, higher serum urate levels predicted poor outcome (dead or in care) and higher vascular event**

rates. The role of urate in stroke pathophysiology remains uncertain, but intervention to lower urate may be worth considering

9.Di Yi Jun Yi Da Xue Xue Bao.2002 Jan;22(1):70-1 Serum uric acid in type 2 diabetic patients complicated by stroke. - Guan MP, Xue YM, Shen J,

RESULTS: Male type 2 diabetic **patients with stroke had significantly higher mean levels of serum uric acid than simple diabetic patients**, but such patients of both genders all had lower HDL levels.

***10.Stroke*. 2000;31:2295-2300 : Antioxidant Profile and Early Outcome in Stroke Patients -** Antonio Cherubini, MD; Maria Cristina Polidori, MD; Mario Bregnocchi, MD

Methods—Plasma antioxidants, including water-soluble (vitamin C and uric acid) and lipid-soluble (vitamins A and E) compounds as well as antioxidant enzyme activities in plasma (superoxide dismutase [SOD] and glutathione peroxidase) and erythrocytes (SOD), were measured by high-performance liquid chromatography (antioxidant vitamins) and by spectrophotometry (antioxidant enzymes) in 38 subjects (25 men and 13 women aged 77.267.9 years) with acute ischemic stroke of recent onset (,24 hours) on admission, after 6 and 24 hours, and on days 3, 5, and 7.

Patients with the worst early outcome (death or functional decline) had higher vitamin A and uric acid plasma levels and lower vitamin C levels and erythrocyte SOD activity than those who remained functionally stable.

11.International Journal of Cardiology Volume 71, Issue 1, 30 September 1999, Pages 17-22 : Is hyperuricemia a risk factor of stroke and coronary heart disease among Africans? - B. Longo-Mbenza, E. Lukoki Luila, Phanzu Mbete and E. Kintoki Vita

Methods: This is a longtitudinal study in a small random number (418) of patients in Kinshasa, Congo

Conclusion: Our results indicate **that hyperuricemia among african patients is a strong predictor of myocardial infarction in men, stroke in both sexes and all causes of mortality in women**

***12.Stroke*. 1998;29:635-639 : Serum Uric Acid Is a Strong Predictor of Stroke in Patients With Non–Insulin-Dependent Diabetes Mellitus** - Seppo Lehto, MD; Leo Niskanen, MD; Tapani Ro¨nnemaa, MD; Markku Laakso, MD

Methods—In this population-based study, cardiovascular risk factors were determined in 1017 patients (551 men and 466 women) with NIDDM, aged

45 to 64 years at baseline. The patients were followed up for 7 years with respect to stroke events.

Conclusions—**Our results indicate that hyperuricemia is a strong predictor of stroke events in middle-aged patients with NIDDM**

AIMS OF THE STUDY

AIMS OF THE STUDY

The study is conducted to study the association between Serum Uric Acid (SUA) and acute ischaemic nonembolic stroke and to assess its risk factor potential using statistical analysis.

To also study the association between Serum Uric Acid (SUA) and other risk factors namely hypertension**,** Diabetes mellitus, CAD and adverse lipid profile**.**

MATERIALS AND METHODS

MATERIALS AND METHODS

INCLUSION CRITERIA :

1. Patients who were admitted in our hospital with first-ever-in life time acute ischaemic nonembolic stroke with or without CT Scan evidence of infarction within 24 hrs of onset of stroke

EXCLUSION CRITERIA :

1. Patients with previous history of TIA / CVA
2. Patients who are on thiazide diuretics
3. Patients who are known cases of gout or show clinical evidences of gout.
4. Patients with chronic renal failure
5. Patients whose CT scan show haemorrhage or other space occupying lesions other than infarct.
6. Patients who were of known cardiac diseases which could be sources of emboli or whose echocardiogram shown sources of emboli.
7. Patients with haemotological abnormalities like leukemia or other myeloproliferative disorders.

A total of 100 patients (50 males and 50 females) with acute stroke who met the criteria , admitted in GRH , MMC, Madurai from 01. 01 .2007 to 31. 10. 2007 were randomly selected and included in this study.

All subjects gave informed consent and the study protocol was approved by the Ethical Committee.

The blood samples were taken within 24 hrs of onset of stroke and sent for biochemical analysis and were analyzed in our Biochemical Laboratory using standard analyzer. The patients were further evaluated for the presence of additional risk factors as follows, using the below mentioned parameters**.**

1. HYPERTENSION :

a) known case of hypertension

b) Blood pressure more than 140 mm of hg systolic and / or more than 90 mm of hg diastolic (62)

2. DIABETES MELLITUS:

a) known case of diabetes mellitus

b) random or postprandial blood sugar more than 200 mgs /dl and / or fasting blood sugar more than 125 mgs /dl(63)

c) The patients with blood sugar values of IFG or IGT were not included as diabetics in this study.

3. CORONARY ARTERY DISEASE :

Patients with ECG evidence of old infarction or Echocardiogram showing regional wall motion abnormalities**.**

4. ADVERSE LIPID PROFILE(64) :

- Total cholesterol - more than 200 mgs/dl
- Triglycerides - more than 150 mgs/dl
- LDL-C - more than 130 mgs/dl
- HDL-C - less than 40 mgs/dl

5. SMOKING AND ALCOHOLISM:

History of smoking and alcoholism within the last 5 yrs have been taken as smokers and alcoholics.

Statistical Tools

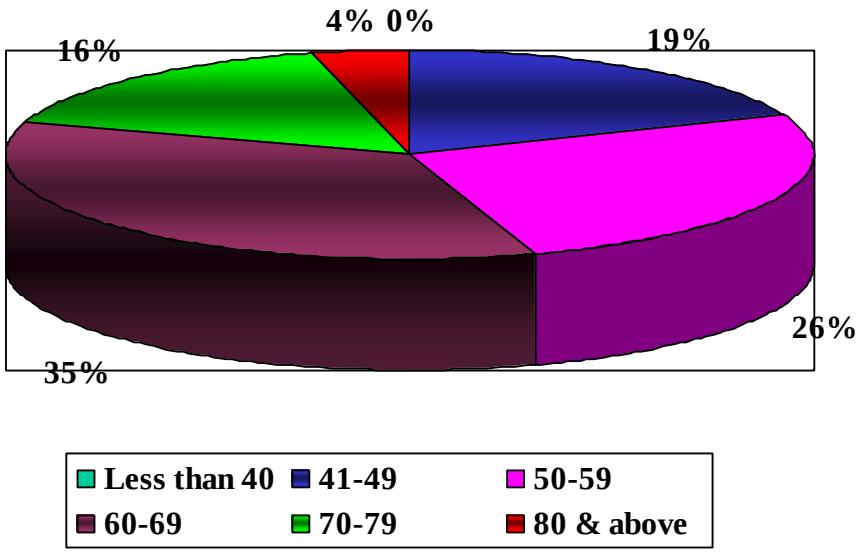
The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer using Epidemiological Information Package (EPI 2002).

Using this software, frequencies, percentage, mean, standard deviation, x^2 and 'p' values were calculated. A 'p' value less than 0.05 is taken to denote significant relationship.

OBSERVATIONS AND RESULTS

FIGURE 1

AGE DISTRIBUTION



OBSERVATIONS AND RESULTS

The observations made in this study are categorized, analysed and tabulated as under:

1. **AGE DISTRIBUTION :**

In this prospective study, 41 to 84 yrs old patients are included.

Table 1.1 : Age Distribution

Age in years	**Cases**	
	No	**%**
Less than 40	-	-
41- 49	19	19
50 – 59	26	26
60 – 69	35	35
70 – 79	16	16
80 & above	4	4
Total	100	100
Mean S.D	59.8 yrs 10.6	

Majority of this stroke population are between 50 to 69 yrs old, (61 % of the population) with 33 Males and 28 females. The elderly population,

above 70 yrs old constitute 20 % of the population with 9 males and 11 females.

Table 1.2 : Age Distribution according to sex

Age in years	Cases			
	Males		Females	
	No.	%	No.	%
Less than 40	-	-	-	-
41- 49	8	16	11	22
50 – 59	20	40	6	12
60 – 69	13	26	22	44
70 – 79	7	14	9	18
80 & above	2	4	2	4
Total	50	100	50	100
Mean S.D	59.1 10.2		60.5 11.1	
'p'	0.2924 Not significant			

The mean age of the male population is 59.1yrs and of the female population is 60.5 yrs. The overall mean age of the study population is 59.8 yrs.

2.RISK FACTORS:

Table 2.1 : Risk Factors

Risk Factor	Cases	
	No	**%**
a) Hypertension		
Present	65	65
Absent	35	35
b) DM		
Present	51	51
Absent	49	49
c) Smoking (among males)		
Present	34	68
Absent	16	32
d) CAD		
Present	32	32
Absent	68	68
e) Hyper lipid		
Present	34	34
Absent	66	66
f) Alcoholism (among males)		
Alcoholic	16	32
Non Alcoholic	31	62
Occasional Drinker	3	6

- Hypertension constitutes the major risk factor in this stroke population as 65 % of the population is hypertensive. 34 males and 31 females are hypertensives and form 68 % and 62 % in their respective population.

- Diabetes mellitus ranks second as a risk factor, constitute 51% of the study population with 23 (46 %) males and 28 (56 %) females.

- Coronary Artery Disease is associated in 32 % of the population with 15 (30 %) males and 17 (34 %) females.

- 34 % of the stroke population has adverse lipid profile and both sexes share equal number of hyperlipidemics (17 each).

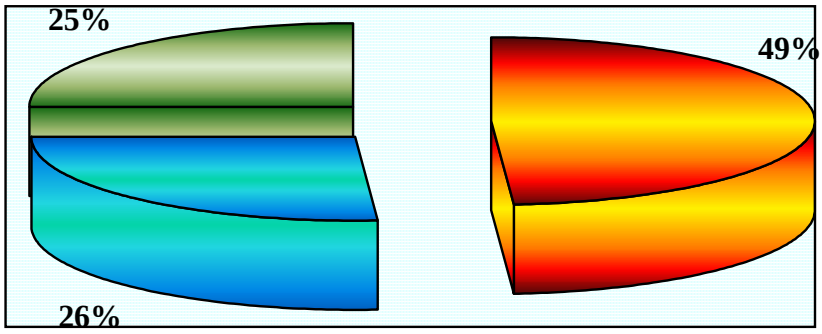
- Among the male population, 34 (68 %) are smokers and 16 (32 %) are alcoholics.

Table 2.2 : Risk Factors according to sex

Risk Factor	Cases			
	Males		Females	
	No.	%	No.	%
a) Hypertension				
Present	34	68	31	62
Absent	16	32	19	38
b) DM				
Present	23	46	28	56
Absent	27	54	22	44
c) Smoking (among males)				
Present	34	68	-	-
Absent	16	32	50	100
d) CAD				
Present	15	30	17	34
Absent	35	70	33	66
e) Hyper lipid				
Present	17	34	17	34
Absent	33	66	33	66
f) Alcoholism (among males)				
Alcoholic	16	32	-	-
Non Alcoholic	31	62	50	100
Occasional Drinker	3	6	-	-

FIG 3

URIC ACID DISTRIBUTION



3.Uric acid levels and their association with risk factors:

The distribution of uric acid levels in the study population are as under:

- Less than 5 mg / dl – 49 % **(**25 males and 24 females)
- Between 5 – 6.9 mg / dl - 26 % **(** 13 males and 13 females)
- Above and equal to 7 mg / dl - 25 % (12 males and 13 females).

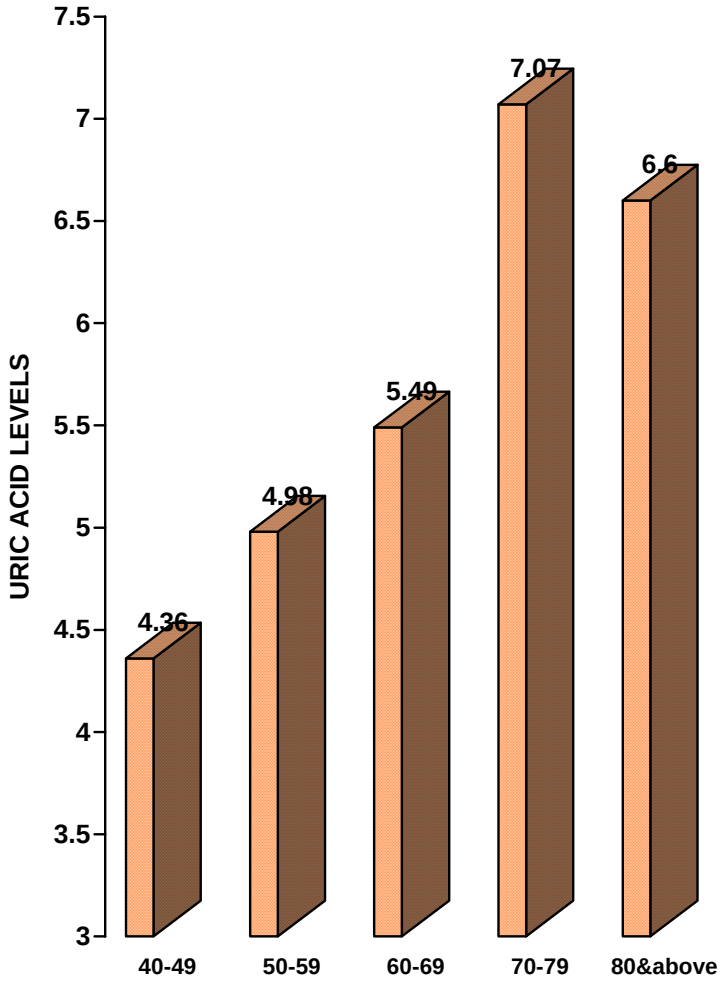
Table 3. A. : Uric Acid (mg/dl)

Uric Acid (mg/dl)	**Cases**			
	Males		**Females**	
	No.	**%**	**No.**	**%**
Less than 5	25	50	24	48
5 – 6.9	13	26	13	26
7 & Above	12	24	13	26
Total	50	100	50	100
Mean S.D	5.41 1.88		5.47 1.53	
'p'	0.6586 Not significant			

Mean uric acid level in males is 5.41 mg / dl and in females it is 5.47 mg / dl.

FIG 3.1.1

AGE AND URIC ACID LEVELS



3.1.AGE AND URIC ACID:

Table 3.1.1 : Age and uric acid

Age group	Uric Acid mg /dl	
	Mean	**S.D**
40 – 49	4.36	1.2
50 – 59	4.98	1.47
60 –69	5.49	1.5
70 –79	7.07	1.7
80 & above	6.6	2.14
'p'	**0.0001 (Significant)**	

Age wise distribution of uric acid is found statistically significant. As age advances the uric acid level also rises with the 'P 'value of 0.0001. This significance is maintained even when male and female populations are considered separately. ('P ' of 0.0056 for males and 0.0077 for females).

Table 3.1.2 : Age and uric acid according to sex

Age group	Uric Acid			
	Males		Females	
	Mean	S.D.	Mean	S.D.
40 – 49	4.19	1.72	4.48	0.7
50 – 59	5.0	1.54	4.92	1.3
60 –69	5.42	1.53	5.54	1.51
70 –79	7.1	2.1	7.04	1.45
80 & above	8.4	-	4.8	0.85
'p'	**0.0056 Significant**		**0.0077 Significant**	

The mean uric acid value for 40 – 49 yrs group is 4.36 mg /dl while the elderly age group of above 70 yrs has the mean value 7.07 mg / dl.

3.2 : SEX AND URIC ACID :

Table 3.2.1 : Sex and uric acid level

Sex	**Uric Acid (mg / dl)**	
	Mean	**S.D**
Males	5.41	1.88
Females	5.47	1.53
'p'	0.6586 (Not significant	

There is no statistically significant association is found in this study between sex and uric acid. The mean uric acid level among male population is 5.41 mg / dl and among female population it is 5.47 mg / dl.

3.3 HYPERTENSION AND URIC ACID:

Table 3.3.1 : Hypertension and uric acid

Hypertension	Uric Acid (mg/ dl)	
	Mean	**S.D**
Present	5.64	1.7
Absent	5.06	1.68
p	0.0793 (Not significant)	

This study does not show any significant association between hypertension and uric acid. The mean uric acid level in hypertensive population is 5.64 mg / dl and in non hypertensive population is 5.06 mg/ dl.

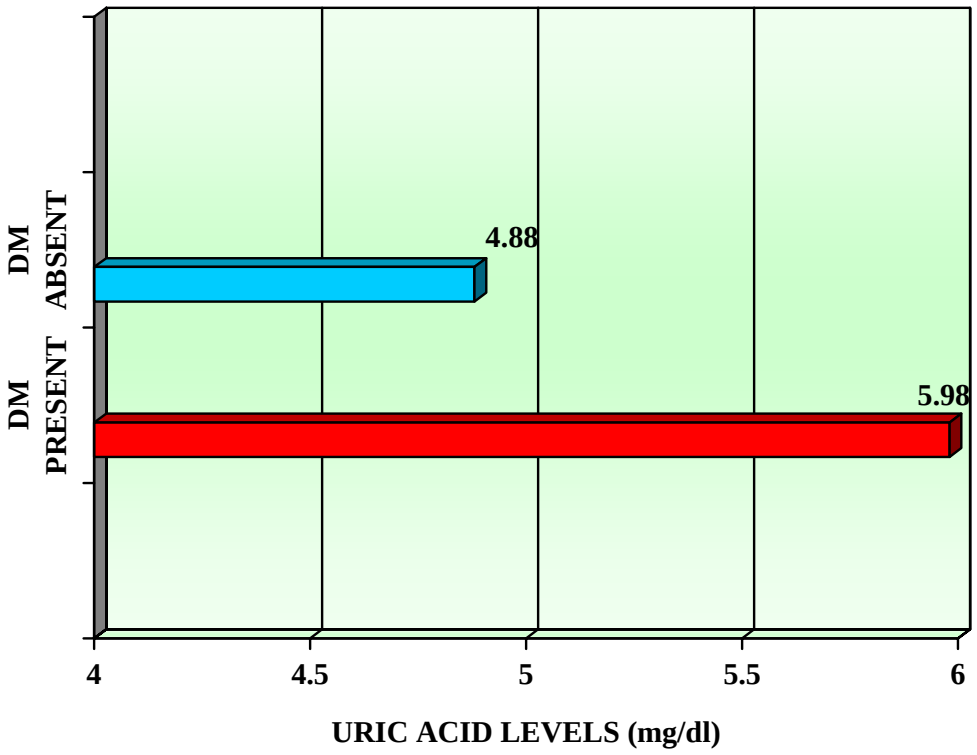
Table 3.3.2 : Hypertension and uric acid –sex wise

Hypertension	Uric Acid (mg / dl)			
	Males		Females	
	Mean	S.D	Mean	S.D
Present	5.49	1.76	5.82	1.64
Absent	5.24	2.18	4.91	1.15
p	0.3706 Not Significant		0.0763 Not Significant	

There is no significant association found, also when males and females are considered separately. The mean uric acid levels for male hypertensives is 5.49 mg/ dl (non hypertensive males- 5.24 mg / dl) and in females is 5.82 mg /dl (non hypertensive females – 4.91 mg / dl).

FIGURE 3.4

DIABETES MELLITUS AND URIC ACID



3.4: DIABETES MELLITUS AND URIC ACID :

Table 3.4.1 : DM and uric acid

DM	Uric Acid (mg / dl)	
	Mean	**S.D**
Present	5.98	1.66
Absent	4.88	1.59
p	**0.0006 (Significant)**	

There is a statistically significant association (p value- 0. 0006) found between the level of uric acid and Diabetes mellitus. Among diabetics the mean uric acid value is 5.98 mg / dl while among non diabetics it is 4.88 mg / dl.

Table 3.4.2 : DM and uric acid according to sex

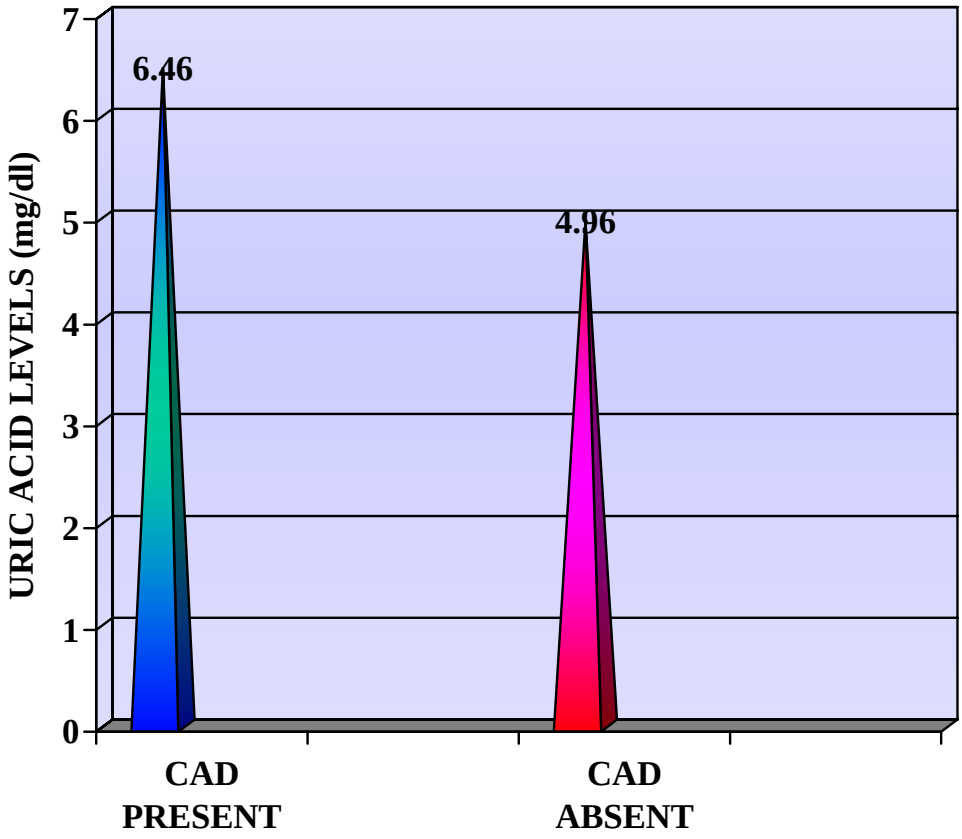
DM	Uric Acid (mg / dl)			
	Males		Females	
	Mean	S.D	Mean	S.D
Present	6.16	1.86	5.83	1.49
Absent	4.76	1.68	5.03	1.8
p	**0.0095** **Significant**		0.0525 Not Significant	

This association is more significant among males (p value -0.0006) among whom the diabetics have 6.16 mg / dl as mean uric acid level compared to non diabetics, 4.76 mg / dl as mean value.

But, this association is not found significant in female population. The mean uric acid level in diabetic women is 5.83 mg / dl when compared to non diabetic women is 5.03 mg / dl .

Fig 3.5.1

CAD AND URIC ACID LEVELS



3.5 : CAD and Uric acid :

Table 3.5.1 : CAD and Uric acid

CAD	**Uric Acid (mg / dl)**	
	Mean	**S.D**
Present	6.46	1.87
Absent	4.96	1.4
p	**0.0004 (Significant)**	

In this study, mean uric acid level in this stroke population with CAD is 6.46 mgs / dl and in those without CAD is 4.96 mgs / dl and thus establishes a statistically significant relationship (‘p’ 0. 0004).

Table 3.5.2 : CAD and Uric acid according to sex

CAD	Uric Acid (mg / dl)			
	Males		Females	
	Mean	S.D	Mean	S.D
Present	6.98	1.72	5.99	1.93
Absent	4.73	1.53	5.21	1.23
p	**0.0003** **Significant**		0.1659 Not Significant	

When males and females are considered, males have a significant association with a ‘p’ value of 0. 0003. Female population does not show such association. (See table)

3.6:Hyperlipidemia and uric acid :

Table 3.6.1 : Hyperlipidemia and Uric acid

Hyperlipidemia	Uric Acid (mg / dl)	
	Mean	**S.D**
Present	5.75	1.9
Absent	5.28	1.59
p	0.2541 (Not significant)	

Mean uric acid level in hyperlipidemic stroke population is 5.75 mgs / dl and compared to 5.28 mgs / dl mean uric acid level in patients with out hyperlipidemia do not show any statistically significant relationship.

Table 3.6.2 : Hyperlipidemia and Uric acid according to sex

Hyperlipidemia	**Uric Acid (mg / dl)**			
	Males		**Females**	
	Mean	**S.D**	**Mean**	**S.D**
Present	5.67	2.16	5.84	1.67
Absent	5.27	1.74	5.29	1.44
p	0.7121 Not significant		0.3399 Not significant	

There is no statistically significant relationship even when males and females are analysed separately.

3.7 : Smoking and uric acid :

Table 3.7.1 : Smoking and Uric acid

Smoking	**Uric Acid (mg / dl)**	
	Mean	**S.D**
Present	5.14	1.8
Absent	5.96	1.98
p	0.0978 Not significant	

Mean uric acid level in smokers is 5.14 mg / dl and among non-smokers is 5.96 mgs / dl. Thus in this study there is no statistically significant relationship between smoking and uric acid.

4. RISK FACTORS IN POPULATION WITH HIGH URIC ACID LEVEL (ie.. > 7mgs / dl)

Table 4.1 : Risk Factors and uric acid levels < / > 7 mgs / dl

Risk Factor	**Uric acid**			
	< 7mg/dl		**> 7mg/dl**	
	No.	**%**	**No.**	**%**
a) Hypertension				
Present	45	60	20	80
Absent	30	40	5	20
'p'	0.1156 Not significant			
b) DM				
Present	34	45.3	17	68
Absent	41	54.7	8	32
'p'	0.0832 Not significant			
c) Smoking (among males)(50)				
Present	27	71.1	7	58.3
Absent	11	28.9	5	41.7
'p'	0.314 Not significant			
d) CAD				
Present	15	20	17	68
Absent	60	80	8	32
'p'	**0.0001 Significant**			

Risk Factor	Uric acid			
	< 7mg/dl		> 7mg/dl	
	No.	%	No.	%
e) Hyper lipid				
Present	22	29.3	12	48
Absent	53	70.7	13	52
'p'	0.1436 Not significant			
f) Alcoholism (among males)				
Alcoholic	15	39.5	4	33.3
Non Alcoholic	23	60.5	8	66.7
'p'	0.6858 Not significant			
No risk factor	7	9.3	2	8
At least one risk factor	68	90.7	23	92
'p'	0.6008 Not significant			
Age				
>65	11	42.3	15	57.7
<65	64	86.5	10	13.5
'p'	**0.0001 Significant**			

Further analysis is done to analyse the relationship between uric acid levels less than and more than 7 mgs / dl and the risk factors. This analysis shows age more than 65 yrs and CAD have statistically significant relationship with uric acid level.

DISCUSSION

DISCUSSION

In this prospective study of 100 stroke population, males and females are equal in number (50 each) and hence there is no sex bias. Further analysis shows the mean age, (males-59.1yrs, females-60.1 yrs) and mean level of uric acid (males- 5.41mgs / dl, females- 5.47 mgs / dl) are similar. Distribution of risk factors also is of in more or less similar pattern (Hypertension: males-34,females-31; Diabetes mellitus: males-23, females-28; CAD: males-15 females-17 ; Hyperlipidemia ; males-17, females- 17). Different studies (9,12) show high mean uric acid level in male population which is not found in this study.

But, in elderly population, both sexes show high level of uric acid which has statistical significance. Regarding the association between risk factors and both sexes, CAD is significantly associated with high uric acid levels in both sexes whereas DM is associated only with males and not with females.

In this study, most of the population belongs to anterior circulation territory, especially of middle cerebral artery region with commonest presentation being hemiplegia , except in one patient with bilateral cerebellar infarct evidenced in MRI scan. As most of the posterior circulation strokes

have masquerading clinical presentations and often lack CT scan evidences of infarction, they are not included in this study to avoid inclusion bias.

Age is the most common non-modifiable risk factor for the development of stroke (14). In this study, 25 % of the population are above 65 yrs with 12 males and 13 females. One pilot study (9) of 163 patients above 70 yrs studied the association of SUA and stroke concludes that SUA is associated with an increased risk for acute ischaemic / nonembolic stroke in elderly patients independently of concurrent metabolic derangements. This study also shows evidences for a significant association between SUA and elderly stroke population, and the association was maintained even when both sexes are considered separately. Thus this study supports the association of high SUA and acute ischaemic / nonembolic stroke.

Hypertension is the most common modifiable risk factor for stroke (14). SUA is also commonly associated with hypertension (65,66). Elevated SUA level is an independent predictor of hypertension in 25 % of patients with new onset , untreated primary hypertension.(21). In this study, H**y**pertension constitutes the major risk factor as 65 % of the stroke population is hypertensive. The mean uric acid level of hypertensive population is 5.64 mgs / dl and of nonhypertensive is 5.06 mgs / dl and thus

this study does not show any statistically significant relationship between SUA and hypertension.

Diabetes mellitus ranks second as a risk factor in this study, constitute 51 % of the study population. One population based study(6)involving 1017 persons with NIDDM, concludes that hyperuricemia is a strong predictor of stroke events in middle aged persons with NIDDM, independently of other CV risk factors. SUA levels are often increased in subjects with MetS (47-49). In this study, with the mean SUA level of 5.98 mgs / dl among diabetics and 4.88 mgs / dl among non-diabetics there is a strong association between SUA and DM. Further analysis shows this association is more stronger among males (mean SUA in male diabetics -6.66 mgs / dl vs non-diabetic males-4.76 mgs / dl)than females. Thus this study strongly favours for an association between SUA and acute ischaemic / nonembolic stroke in diabetic population.

SUA is significantly associated with cardiovascular mortality in certain epidemiological studies (13). One population based cohort study(67), with a follow up of 8.4 yrs, comprising 4385 participants of the Rotterdam study concludes that SUA is a strong risk factor for myocardial infarction and stroke. In this study CAD is found in 32 % of the patients with 15 males and 17 females. The mean SUA level in this CAD population is 6.46 mgs / dl

comparing this to patients without CAD is 4.96 mgs / dl which shows a strong statistical significance. Among those 32 stroke patients with CAD 17 have SUA > 7 mgs / dl. This also shows a strong statistical significance with a 'p' value of 0.0001. Hence this study strongly favours Rotterdam study and suggests SUA is a strong risk factor for myocardial infarction and stroke.

Several prospective studies (69,70) have shown that higher levels of total cholesterol increase the risk of ischaemic stroke. Furthermore a meta-analysis of 90000 patients (61) showed that administration of statins reduces the risk of stroke among patients with CAD and that this risk reduction is primarily related to the extent to which LDL-C levels are lowered. In some studies (71,72) relating Met S and SUA, increased SUA levels correlated with low HDL-C levels.

In our study, Hyperlipidemia is considered separately and not as a part of Met S. Moreover, most of our patients in this study population are from low socio-economic group and are not found obese. In this study, the mean uric acid level in hyperlipidemic patients is 5.75 mgs / dl and in patients without hyperlipidemia is 5.28 mgs / dl and does not show any significant association between these variables. Out of 34 patients with hyperlipidemia in this study, only 12 are found to have SUA > 7 mgs / dl.

Among the other risk factors like smoking and alcoholism, they are not considered as separate risk factors in many pilot studies of this kind. This study also fails to show any statistically significant relationship between SUA and these risk factors when considered separately.

Further analysis between < 7 mgs / dl and > 7 mgs / dl SUA groups also maintain the association between high SUA and the risk factors namely age and CAD.

CONCLUSION

CONCLUSION

1) This study shows that elevated SUA is strongly associated with an increased risk for the development of acute ischaemic/ non-embolic stroke in this study population.

2) The association between elevated SUA and ischaemic stroke may need to be considered especially when treating elderly patients, diabetics and the population with coronary artery disease.

3) Elevated SUA can be considered as one of the risk factors for acute ischaemic non-embolic stroke.

4) Lowering of SUA level can be considered as one of the preventory modalities for stroke while treating high risk population.

5) It is also suggested that further studies are required to assess whether lowering of SUA level with drugs can actually reduce the risk of ischaemic stroke.

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APPENDIX I - APPROVAL FROM ETHICAL COMMITTEE

Govt. Rajaji Hospital,
Madurai – 625 020. Dt. 15.03.2007

Sub: Establishment of GCMH, Rajaji Hospital, Madurai – Ethical Committee
Projects approved by the Committee – Intimation – Sent – Reg.

The Ethical Committee of the Govt. Rajaji Hospital, Madurai was held at 12.30 pm on 15.03.2007 at the Dean's Chamber, Govt. Rajaji Hospital, Madurai, and the following Projects were approved unanimously by the Committee Members.

S.No	Name of the Student	Name of the Project approved
01)	Dr. D. BASKARAN, PG IN Paediatric Surgery.	The efficacy and safety of topical application of collagen for the treatment of Omphalocele.
02)	Dr. P. Kannan, DM PG in Cardiology.	Echo Cardiographic evaluation of HIV infected persons.
03)	Dr. R. Sankar, MD PG in General Medicine.	Prevalence of Hepato pulmonary syndrome in chronic liver disease.
04)	Dr.P. Ramanathan, MD PG in General Medicine.	Serum Uric acid – an independent risk factor in acute non-embolic ischemic stroke.

Please note that the investigator should adhere the following:-

01) She/He should get a detailed informed consent from the patients/participants and maintain confidentially.
02) She/He should carry out the work without detrimental to regular activities as well as without extra expenditure to the Institution or Government.
03) She/He should inform the Institution Ethical Committee in case of any change of study procedure site and investigation or guide.
04) She/He should not deviate for the area of the work for which applied for Ethical clearance.
05) She/He should inform the IEC immediately, in case of any adverse events or serious adverse reactions.
06) She/He should abide to the rules and regulations of the Institution.
07) She/He should complete the work within the specific period and apply for, if any extension of time is required. She should apply for permission again and do the work.
08) She/He should submit the summary of the work to the Ethical Committee on completion of the work.
09) She/He should not claim any funds from the Institution while doing the work or on completion.
10) She/He should understand that the members of IEC have the right to monitor the work with prior intimation.

16/3/07.

Dean/Chairman,
Ethical Committee, Govt. Rajaji Hospital, Madurai.

16/3/07

To
The above Members through the Concerned HODs.

1) Thro prof + HOD of Paediatric Surgery
2) Thro prof + HOD of Cardiology
3) Thro prof + HOD of General Medicine

} GRH, Madurai

Forwarded
Letter

PROFESSOR AND HEAD
DEPARTMENT OF MEDICINE
MADURAI MEDICAL COLLEGE
MADURAI-625 020.

APPENDIX II – PROFORMA

PROFORMA

CASE NO

Name:

Age: Sex: M/F

Address:

occupation: Income:

Socioeconomic status: Handedness: R / L

DOA: DOD:

PRESENT COMPLAINTS:

H / O Present illness:

Duration- Seizures: Y / N ICT Features; Y / N

H / O LOC : Y / N

S/O higher functions abnormality :

s/o cranial nerve lesions:

s/o motor system abnormalities:

s/o sensory involvement:

s/o cerebellar involvement:

s/o EPS involvement:

PAST HISTORY

- HTN-Y/N DM –Y/N CAD-Y/N CVA-Y/N TIA-Y/N

GOUT-Y/N Hyperlipidemia –Y/N

PERSONAL HISTORY

SMOKING- ALCOHOLISM

DIET- Veg/ Non veg/ mixed DRUG INTAKE- Thiazide diuretic

FAMILY HISTORY

DM- ;HTN ;CAD ;TIA ;CVA ;GOUT .

CLINICAL EXAMINATION:

(a) VITALS: Pulse- /mt; BP- mm of Hg

(b)Higher functions; Consciousness;

Memory :

Speech :

Behaviour

(c) Cranial nerves ;

(d) SPINOMOTOR SYSTEM: R L

1.Bulk of muscle UL

LL

2.Tone UL

LL

3.Power UL

LL

4.DTR UL

LL

5.Plantar -

(e) SENSORY SYSTEM

(f) CEREBELLUM :

(g) EPS :

(h) SPINE / CRANIUM ;

OTHER SYSTEMS ;

(a) CVS :

(b) RS :

(c) P / A ;

DIAGNOSIS- CVA – Anterior circulation

Posterior circulation

Territory- ACA / MCA

INVESTIGATIONS :

1.Blood : TC - cells/cu.mm

DC- P L M E %

Hb- gms/dl

2. Urine : Alb –

Sug-

Dep-

3.Blood : Sugar- mgs/dl

Urea-

Creatinine

4. Lipid profile:TCL mgs/dl

LDL

HDL

TGS

5. SERUM URIC ACID-

6.ECG in all leads -

7.CT Brain Plain - INFARCT REGION -

INFARCT SIZE -

8.CARDIAC EVALUATION -

APPENDIX III- MASTER CHART

MASTER CHART

Sl.No	AGE	SEX	HTN	DM	SMOKING	CAD	HYPER	ALCOHOLISM	DIET	URIC ACID (MD/Dl)		
										< 5	5 - 6.9	>7
1	45	Male	Absent	Absent	Yes	Absent	Present	Occasional	Mixed	3.4	-	-
2	80	Male	Absent	Absent	Yes	Absent	Absent	No	Mixed	-	-	8.4
3	48	Male	Absent	Absent	Yes	Absent	Present	Yes	Mixed	2.6	-	-
4	51	Male	Absent	Absent	Yes	Absent	Absent	No	Mixed	4.2	-	-
5	56	Male	Present	Present	Yes	Absent	Present	No	Mixed	-	6.2	-
6	55	Female	Absent	Absent	No	Absent	Absent	No	Mixed	4.3	-	-
7	78	Male	Present	Present	No	Present	Absent	No	Mixed	-	-	8.1
8	65	Female	Absent	Present	No	Present	Present	No	Mixed	4.6	-	-
9	60	Male	Present	Absent	No	Absent	Present	No	Mixed	4.5	-	-
10	62	Female	Absent	Absent	No	Absent	Absent	No	Mixed	3.9	-	-
11	78	Female	Absent	Present	No	Absent	Absent	No	Mixed	-	5.4	-
12	40	Female	Absent	Absent	No	Absent	Absent	No	Mixed	4.2	-	-
13	65	Male	Absent	Present	No	Absent	Absent	No	Mixed	-	6	-
14	50	Male	Present	Absent	Yes	Absent	Absent	No	Mixed	-	5.2	-
15	52	Male	Absent	Absent	Yes	Absent	Absent	No	Mixed	3.6	-	-
16	65	Female	Present	Present	No	Absent	Absent	No	Mixed	-	5.6	-
17	65	Male	Absent	Present	No	Absent	Absent	Yes	Mixed	-	6.3	-
18	50	Male	Present	Absent	No	Absent	Absent	No	Mixed	4.2	-	-
19	75	Male	Absent	Present	No	Present	Present	No	Mixed	-	-	8.4
20	70	Female	Present	Absent	No	Present	Absent	No	Mixed	-	-	7.5
21	62	Male	Present	Present	Yes	Present	Absent	Yes	Mixed	-	6.3	-
22	60	Female	Present	Absent	No	Absent	Absent	No	Mixed	4.5	-	-
23	75	Female	Absent	Absent	No	Absent	Absent	No	Mixed	-	-	7.2
24	78	Male	Present	Present	No	Absent	Absent	No	Mixed	-	5.4	-
25	48	Male	Absent	Absent	No	Absent	Absent	No	Mixed	4	-	-
26	65	Female	Present	Present	No	Absent	Absent	No	Mixed	-	-	7.2

Sl.No	AGE	SEX	HTN	DM	SMOKING	CAD	HYPER	ALCOHOLISM	DIET	URIC ACID (MD/Dl)		
										< 5	5 - 6.9	>7
27	42	Female	Absent	Absent	No	Absent	Present	No	Mixed	3.8	-	-
28	55	Male	Absent	Absent	Yes	Absent	Absent	No	Mixed	3.9	-	-
29	61	Male	Present	Absent	Yes	Absent	Absent	No	Mixed	-	5.4	-
30	53	Male	Present	Absent	Yes	Absent	Absent	Yes	Non-Vege.	4.4	-	-
31	75	Male	Present	Absent	Yes	Absent	Absent	Yes	Non-Vege.	4.2	-	-
32	47	Male	Present	Present	Yes	Absent	Present	Yes	Non-Vege.	-	-	7.9
33	58	Male	Present	Present	No	Present	Present	No	Vege.	-	-	7.6
34	70	Female	Present	Absent	No	Absent	Absent	No	Non-Vege.	-	-	8.3
35	55	Male	Present	Present	No	Present	Absent	No	Non-Vege.	-	5.2	-
36	64	Female	Present	Present	No	Absent	Absent	No	Non-Vege.	-	3.9	-
37	69	Female	Present	Present	No	Absent	Present	No	Non-Vege.	4.8	-	-
38	40	Female	Present	Present	No	Present	Absent	No	Non-Vege.	3.8	-	-
39	48	Female	Present	Absent	No	Absent	Absent	No	Non-Vege.	4.2	-	-
40	84	Female	Present	Present	No	Present	Absent	No	Vege.	4.2	-	-
41	40	Female	Absent	Present	No	Absent	Absent	No	Non-Vege.	-	5.6	-
42	65	Male	Present	Absent	No	Absent	Absent	No	Non-Vege.	4.7	-	-
43	70	Male	Absent	Absent	No	Absent	Absent	No	Vege.	-	-	9.2
44	65	Male	Present	Present	Yes	Absent	Absent	No	Non-Vege.	-	5	-
45	50	Female	Present	Absent	No	Absent	Absent	No	Non-Vege.	3.6	-	-
46	55	Male	Present	Present	Yes	Absent	Absent	No	Non-Vege.	4.5	-	-

Sl.No	AGE	SEX	HTN	DM	SMOKING	CAD	HYPER	ALCOHOLISM	DIET	URIC ACID (MD/Dl)		
										< 5	5 - 6.9	>7
47	70	Female	Present	Present	No	Present	Present	No	Vege.	-	-	9
48	62	Female	Present	Absent	No	Absent	Absent	No	Non-Vege.	4.4	-	-
49	73	Male	Present	Present	No	Absent	Absent	No	Vege.	-	5.2	-
50	60	Male	Present	Absent	Yes	Present	Absent	Yes	Non-Vege.	-	-	8.6
51	40	Female	Absent	Absent	No	Absent	Absent	No	Non-Vege.	3.7	-	-
52	47	Male	Absent	Present	No	Absent	Present	No	Vege.	4.8	-	-
53	52	Male	Present	Absent	Yes	Absent	Absent	Yes	Non-Vege.	4.2	-	-
54	62	Male	Present	Absent	No	Absent	Absent	Yes	Non-Vege.	2.6	-	-
55	56	Male	Absent	Present	Yes	Present	Present	Yes	Non-Vege.	-	-	8
56	55	Male	Present	Absent	Yes	Present	Absent	Yes	Non-Vege.	-	6.3	-
57	60	Female	Present	Absent	No	Present	Absent	No	Non-Vege.	-	-	7.4
58	60	Female	Absent	Present	No	Present	Present	No	Non-Vege.	-	6.8	-
59	57	Male	Present	Absent	Yes	Absent	Absent	Yes	Non-Vege.	-	5.8	-
60	53	Male	Absent	Absent	Yes	Absent	Absent	Yes	Non-Vege.	2.8	-	-
61	42	Male	Present	Absent	Yes	Absent	Present	No	Non-Vege.	4.4	-	-
62	58	Male	Present	Present	Yes	Absent	Absent	Yes	Non-Vege.	3.8	-	-
63	75	Male	Present	Present	No	Present	Absent	No	Vege.	-	-	9.2
64	58	Male	Present	Present	Yes	Present	Present	No	Non-Vege.	-	-	8.2
65	65	Female	Absent	Present	No	Absent	Absent	No	Non-Vege.	-	5.8	-

Sl.No	AGE	SEX	HTN	DM	SMOKING	CAD	HYPER	ALCOHOLISM	DIET	URIC ACID (MD/Dl)		
										< 5	5 - 6.9	>7
66	60	Female	Present	Present	No	Absent	Present	No	Vege.	-	6.2	-
67	58	Female	Present	Present	No	Present	Present	No	Vege.	-	-	7.4
68	80	Female	Present	Absent	No	Absent	Absent	No	Vege.	-	5.4	-
69	68	Female	Present	Present	No	Present	Present	No	Non-Vege.	-	-	8.8
70	55	Female	Absent	Present	No	Absent	Present	No	Non-Vege.	4.6	-	-
71	62	Female	Present	Present	No	Present	Present	No	Non-Vege.	3.8	-	-
72	45	Female	Absent	Absent	No	Absent	Absent	No	Non-Vege.	-	5.4	-
73	45	Female	Absent	Present	No	Absent	Present	No	Non-Vege.	4.2	-	-
74	68	Female	Present	Absent	No	Absent	Absent	No	Non-Vege.	4.2	-	-
75	71	Female	Present	Present	No	Present	Absent	No	Non-Vege.	-	-	7.2
76	57	Male	Present	Present	Yes	Absent	Absent	Yes	Non-Vege.	3.8	-	-
77	62	Female	Present	Present	No	Present	Present	No	Non-Vege.	-	-	7
78	48	Female	Present	Present	No	Present	Absent	No	Non-Vege.	4.8	-	-
79	55	Female	Present	Absent	No	Absent	Absent	No	Non-Vege.	4.6	-	-
80	50	Female	Present	Present	No	Present	Present	No	Vege.	-	5	-
81	58	Male	Present	Absent	Yes	Absent	Absent	No	Non-Vege.	3.8	-	-
82	49	Female	Absent	Present	No	Absent	Present	No	Non-Vege.	-	5.4	-
83	64	Female	Absent	Present	No	Absent	Absent	No	Non-Vege.	-	6.6	
84	48	Female	Absent	Present	No	Absent	Present	No	Non-Vege.	4.2	-	-

Sl.No	AGE	SEX	HTN	DM	SMOKING	CAD	HYPER	ALCOHOLISM	DIET	URIC ACID (MD/Dl)		
										< 5	5 - 6.9	>7
85	68	Female	Present	Present	No	Absent	Present	No	Non-Vege.	-	-	7.2
86	65	Female	Absent	Absent	No	Absent	Absent	No	Non-Vege.	4.8	-	-
87	63	Male	Present	Present	Yes	Present	Present	Occasional	Non-Vege.	3.8	-	-
88	65	Female	Present	Absent	No	Absent	Absent	No	Non-Vege.	-	5.2	-
89	40	Male	Absent	Absent	Yes	Present	Present	No	Non-Vege.	4	-	-
90	80	Male	Present	Present	Yes	Present	Present	Yes	Non-Vege.	-	-	8.4
91	50	Male	Absent	Absent	Yes	Absent	Absent	No	Non-Vege.	4.2	-	-
92	47	Male	Present	Present	Yes	Absent	Present	No	Non-Vege.	2.4	-	-
93	66	Female	Absent	Absent	No	Present	Absent	No	Non-Vege.	2.8	-	-
94	72	Female	Present	Absent	No	Present	Absent	No	Vege.	4.2	-	-
95	70	Female	Present	Absent	No	Absent	Absent	No	Non-Vege.	-	-	7
96	70	Female	Present	Present	No	Present	Absent	No	Non-Vege.	-	-	7.6
97	60	Female	Present	Present	No	Absent	Present	No	Vege.	-	6.4	-
98	62	Male	Present	Present	Yes	Present	Present	No	Non-Vege.	-	-	7.2
99	60	Male	Present	Absent	Yes	Absent	Present	No	Non-Vege.	4.6	-	-
100	68	Male	Present	Absent	Yes	Present	Absent	Occasional	Non-Vege.	-	5.4	-